special article

Annals of Oncology 22: 1973–1980, 2011
doi:10.1093/annonc/mdr313
Published online 4 July 2011

1st ESMO Consensus Conference in lung cancer; Lugano 2010: Small-cell lung cancer

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Received 8 April 2011; revised 11 May 2011; accepted 27 May 2011

The 1st ESMO Consensus Conference on lung cancer was held in Lugano, Switzerland on 21st and 22nd May 2010 with the participation of a multidisciplinary panel of leading professionals in pathology and molecular diagnostics and medical, surgical and radiation oncology. Before the conference, the expert panel prepared clinically relevant questions concerning five areas as follows: early and locally advanced non-small-cell lung cancer (NSCLC), first-line metastatic NSCLC, second-/third-line NSCLC, NSCLC pathology and molecular testing, and small-cell lung cancer (SCLC) to be addressed through discussion at the Consensus Conference. All relevant scientific literature for each question was reviewed in advance. During the Consensus Conference, the panel developed recommendations for each specific question. The consensus agreement in SCLC is reported in this article. The recommendations detailed here are based on an expert consensus after careful review of published data. All participants have approved this final update.
Key words: Consensus, ESMO, SCLC

Lugano 2010: Background to the ESMO Consensus Conference

In 2009, European Society for Medical Oncology (ESMO) decided to update the ESMO clinical recommendations in lung cancer through a consensus process addressing five specific areas:

1 -Early and locally advanced non-small-cell lung cancer (NSCLC)
2 -NSCLC pathology and molecular testing
3 -First-line metastatic NSCLC
4 -Second-/third-line NSCLC
5 -Small-cell lung cancer (SCLC)

Five working groups were appointed, each comprised six to eight participants with multidisciplinary involvement and led by a chair, and with the assistance of one expert in methodological aspects. A total of 39 experts were involved in this consensus process (see Panel members listed in the Appendix).

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[†]See Appendix for members of the Panel.

The 1st ESMO Consensus Conference on Lung Cancer was held in May 2010 in Lugano. Before the conference, each group identified a number of clinically relevant questions suitable for consensus discussion and provided the available literature. At the Conference, in five parallel sessions, each group discussed and reached agreement on the questions previously chosen. Decisions were made using studies published in peer review journals. If no relevant published data were identified, expert opinions were considered. The consideration of abstracts was at the discretion of the groups. All relevant scientific literature, as identified by the experts, was considered. A systematic literature search was not carried out. The recommendations from each group were then presented to all the experts and discussed, and a general consensus was reached. The 'Infectious Diseases Society of American-United States Public Health Service Grading System' was used (shown in Tables 1 and 2) for level of evidence and strength of recommendation for each question raised [1].

The consensus in SCLC is detailed here. SCLC remains an important focus for treatment and research. The SCLC ESMO Guidelines 2010 [2] were endorsed and should be read in conjunction with these additional comments on specific patient situations. Table 3 provides a summary of panel recommendations. The final recommendations listed here have been approved by all participants.

Table 1. Level of evidence [1]

I	Evidence from at least one large randomised control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

Table 2. Strength of recommendation [1]

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,…), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

STAGING ISSUES

1. What is limited stage?

Limited stage should be based on the TNM (tumour–node–metastasis) 7 classification i.e. T1-4 N0-3 M0 [3]. In the new IASLC (International Association for the Study of Lung Cancer) staging system, the largest difference in patient outcomes was observed in patients with N1 versus N2 disease (19 versus 14 months median survival, hazard ratio = 1.40, $P = 0.0001$) [4]. Furthermore, tumour size was of particular prognostic relevance in patients with N0/N1.

Recommendation 1: The new TNM 7 staging system for NSCLC is to be adopted for SCLC.

Strength of recommendation: A

Level of evidence: I

2. Use of FDG–PET

Several studies have suggested that the old distinction between limited and extensive stage can be improved with positron

Table 3. Summary of recommendations

	Recommendations
Staging issues	
Recommendation 1	The new TNM 7 staging system for NSCLC is to be adopted for SCLC
Recommendation 2	The use of PET is not based on randomised trials and treatment decisions should not be based on PET findings alone. PET findings which could modify treatment decisions should be pathologically confirmed
Recommendation 3	For a solitary extrathoracic metastasis based on initial staging examinations, pathologic proof is often not feasible and may delay treatment. Depending on the clinical situation, early response evaluation to initial chemotherapy can be more appropriate in deciding whether a solitary metastasis is likely to be metastatic or not. If bone is the sole metastatic site, magnetic resonance imaging may be preferred to more invasive procedures
Treatment issues	
First-line treatment	
Recommendation 4	In patients with clinical T1-2 N0-1 stage that are potential surgical patients, mediastinal node exploration should be carried out. Surgery may be indicated in patients with no mediastinal involvement, and resection should be followed by chemotherapy. Postoperative radiotherapy should be considered for pathologic N1 and unforeseen N2 disease
Recommendation 5	First-line chemotherapy should be offered to patients with metastatic SCLC and PS 0–2. It may be considered in selected cases in PS 3–4
Recommendation 6	Limited-stage patients with good PS should be considered for concomitant chemoradiotherapy, taking into account the feasibility of radiation treatment plan and good planning target volume coverage while maintaining normal tissue dose constraints
Recommendation 7	Thoracic radiotherapy given either concomitantly or sequentially is currently not recommended in patients with distant metastases that have responded to chemotherapy

Table 3. (*Continued*)

	Recommendations
Recommendation 8	In patients with brain involvement as the only metastatic site responding to chemotherapy, concomitant chemotherapy with thoracic radiotherapy is currently not recommended
Recommendation 9	PCI is recommended for patients with tumour response. Response should be determined by a restaging CT scan
Recommendation 10	PCI in patients who are 65 years or older, requires to balance the benefit and risk of possible neurocognitive impairment to be considered
Follow-up issues	
Recommendation 11	Subsequent follow-up should be at 2–3 months in non-progressing patients at the end of initial treatment and response determination. The actual timing depends on patient circumstances and availability of further treatment. Imaging with CT is preferable
Treatment issues	
Second-line treatment and beyond	
Recommendation 12	Sensitive disease: retreat with the same regimen that induced their initial response, usually reinduction with platinum/etoposide
Recommendation 13	Resistant disease: either oral or i.v. topotecan is recommended for selected patients having resistant relapse, i.e. not amenable to reinduction with first-line treatment
Recommendation 14	Refractory disease and beyond second-line treatment: selected patients with good PS may benefit from further treatment with a chemotherapy agent not previously used
Recommendation 15	Patients, not previously treated with thoracic radiotherapy with a symptomatic recurrence in the mediastinum, such as superior cava vein obstruction or obstructed major airway, may benefit from thoracic radiotherapy
Recommendation 16	Local brain re-irradiation, which may include stereotactic radiotherapy, may be considered in selected patients

emission tomography (PET) and that it has a potential role in adapting target volume for radiotherapy [5–8]. However, histological confirmation of discordant PET findings is not routinely carried out and the current studies have severe limitations as regards pathologic correlation.

Recommendation 2: The use of PET is not based on randomised trials and treatment decisions should not be based on PET findings alone. PET findings, which could modify treatment decisions, should be pathologically confirmed.

Strength of recommendation: C

Level of evidence: III

3. Single M1b

Recommendation 3.1: For a solitary extrathoracic metastasis based on initial staging examinations, pathologic proof is often not feasible and may delay treatment. Depending on the clinical situation, early response evaluation to initial chemotherapy can be more appropriate in deciding whether a solitary metastasis is likely to be metastatic or not.

Strength of recommendation: C

Level of evidence: V

Recommendation 3.2: If bone is the sole metastatic site, magnetic resonance imaging may be preferred to more invasive procedures.

Strength of recommendation: B

Level of evidence: V

TREATMENT ISSUES: FIRST-LINE TREATMENT

The figure shows a treatment algorithm using the new TNM 7 staging classification.

4. Should surgery be considered for any specific subgroup?

Several retrospective reports on surgically treated early SCLC patients indicated relatively favourable outcomes of this approach if there was no mediastinal lymph node involvement [9–11]. Randomised clinical trials addressing the role of surgery and adjuvant chemotherapy versus combined chemoradiotherapy in node-negative SCLC are lacking. The panel believes that these retrospective data are consistent enough to consider surgical approach in selected and adequately staged SCLC patients.

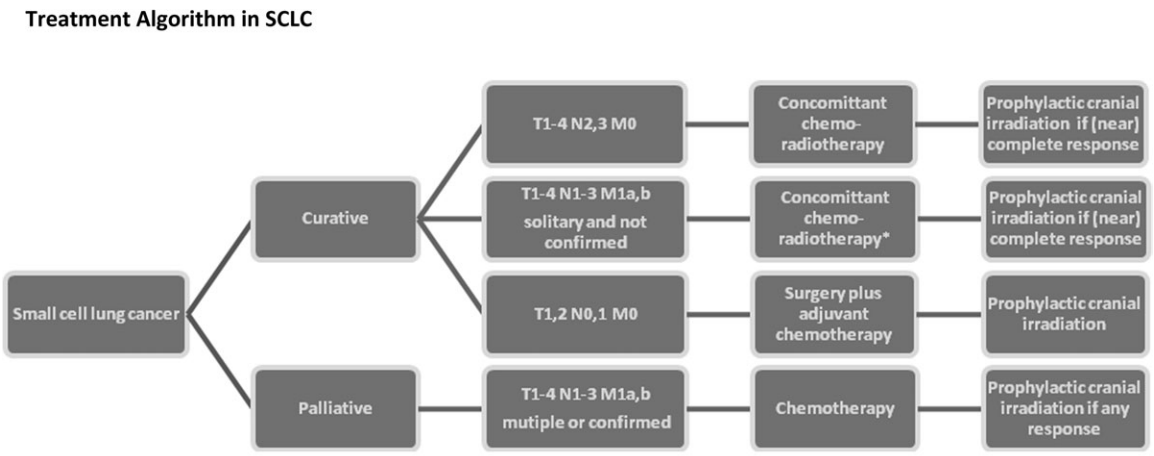
Recommendation 4: In patients with clinical T1-2 N0-1 stage who are potential surgical patients, mediastinal node exploration should be carried out. Surgery may be indicated in patients with no mediastinal involvement; resection should be followed by chemotherapy. Postoperative radiotherapy should be considered for pathologic N1 and unforeseen N2 disease.

Strength of recommendation: C

Level of evidence: V

5. What is the treatment of choice for chemotherapy-naive patients with M1 disease?

Platinum/etoposide chemotherapy is a standard as outlined in the 2010 ESMO recommendations [2]. A recent



meta-analysis has suggested equivalence between irinotecan/platinum and etoposide/platinum in extensive-stage patients and a further study in Caucasian population has suggested that irinotecan/cisplatin is not inferior to etoposide/cisplatin [12, 13].

Recommendation 5: First-line chemotherapy should be offered to patients with metastatic SCLC and performance status (PS) of zero to two (scenario 1). It may be considered in selected cases in PS of three to four (scenario 2).

Strength of recommendation: scenario 1: A; scenario 2: C
Level of evidence: scenario 1: I; scenario 2: V

6. Patient eligibility for early concurrent thoracic radiotherapy on cycle 1 or 2

Patients with good PS are eligible for early concurrent thoracic radiotherapy in cycle 1 or 2 [2, 14]. Computed tomography (CT)-based three-dimensional conformal radiotherapy is recommended. Use of FDG–PET for target volume definition is being evaluated. There is no standard dose that may vary between 45 Gy (twice daily) and 55–70 Gy (once daily). Trials exploring the optimal dose and fractionation are ongoing. There are no specific recommendations for SCLC in terms of normal tissue constraints. Based on NSCLC data, both V20 corresponding to the percentage of normal lung parenchyma receiving 20 Gy and the mean lung dose (MLD) should be recorded as they correlate with the risk of radiation pneumonitis [15]. As target volumes may be large, a V20 level of 35%–40% or an MLD of 20–23 Gy can be considered acceptable, but some patients (~10%–15%) may develop severe radiation-induced toxicity [16]. Recent studies have explored an involved-field approach without elective irradiation [17–19]. Furthermore, in subgroup analysis of prospective trials, elderly patients with good PS seem to have similar outcomes to younger patients and age does not appear to impact on efficacy [20–22]. Toxicity, particularly haematological may be greater among the elderly.

Recommendation 6: Limited-stage patients with good PS should be considered for concomitant chemoradiotherapy, taking into account the feasibility of radiation treatment plan and good planning target volume coverage while maintaining normal tissue dose constraints.

Strength of recommendation: A
Level of evidence: II

7. Other special metastatic situations

A single-centre five-arm randomised study indicated a 5.4% 5-year improvement in a subgroup of patients with metastatic disease who had either a complete or partial response within the thorax and complete remission of distant disease after initial chemotherapy with the use concomitant thoracic radiotherapy and chemotherapy versus chemotherapy alone [23]. The hypothesis generated by this subgroup analysis is being addressed in a phase III multicentre study.

Recommendation 7: Thoracic radiotherapy given either concomitantly or sequentially is currently not recommended in patients with distant metastases that have responded to chemotherapy.

Strength of recommendation: C
Level of evidence: II

8. Brain metastases as the only metastatic site

When the brain is the only documented metastatic site of disease, the use of whole-brain radiotherapy and thoracic radiotherapy in addition to chemotherapy may lead to more favourable results, based on a small retrospective study of 30 patients [24]. Data from a prospective study are needed to support the observation.

Recommendation 8: In patients with brain involvement as the only metastatic site responding to chemotherapy, concomitant chemotherapy with thoracic radiotherapy is currently not recommended.

Strength of recommendation: C
Level of evidence: IV

9. Which patients should be considered for prophylactic cranial irradiation?

Prophylactic cranial irradiation (PCI) is recommended at the end of initial therapy for patients with a tumour response and no contraindications for this procedure. It is important to define tumour response for consideration of PCI [25–27]. Although chest X-ray was most often used in the older trials included in the meta-analysis [25], the panel believes the restaging should be done with the use of CT scan. The imaging should be carried out at 3–4 weeks after the end of initial treatment, as at this stage the determination of tumour response is not yet hampered by the radiotherapy-induced fibrosis.

Recommendation 9: PCI is recommended for patients with tumour response. Response should be determined by a restaging CT scan.

Strength of recommendation: A

Level of evidence: I

10. Role of PCI in older patients

The mean age in the PCI meta-analysis was 59 with 25% of patients being 65 years or older. However, age older than 60–65 is a risk factor for neurocognitive impairment [28, 29].

Recommendation 10: PCI in older patients, 65 years and older, requires to balance the benefit and risk of possible neurocognitive impairment to be considered.

Strength of recommendation: B

Level of evidence: II

FOLLOW-UP ISSUES

11. What is the optimal follow-up?

SCLC is likely to relapse or progress after initial treatment and second-line treatment improves survival in good PS patients [30]. Detecting a relapse or progression before deterioration of PS is therefore a reasonable approach. Long-term survivors may be at risk of second lung cancer that should be histologically confirmed.

Recommendation 11: Subsequent follow-up should be at 2–3 months in non-progressing patients at the end of initial treatment and response determination. The actual timing depends on patient circumstances and availability of further treatment. Imaging with CT is preferable.

Strength of recommendation: C

Level of evidence: V

TREATMENT ISSUES: SECOND-LINE TREATMENT AND BEYOND

The majority of patients with SCLC experience relapse after their initial treatment, with a median survival of 2–3 months without second-line therapy. Although second-line therapy may induce responses in ~10%–40% of patients, these are usually short-lived, and the median survival rarely exceeds 6 months [31].

Three categories of disease have been described in the literature regarding the response to initial therapy and the duration of response: sensitive, resistant, and refractory. 'Sensitive' refers to patients who have had a tumour response lasting 90 days or longer. 'Resistant' refers to patients who have recurred within 90 days of completing therapy. 'Refractory' refers to patients with tumours that never responded to first-line therapy or to those who progressed during first-line therapy [30].

12. Sensitive disease

Patients having sensitive disease relapsing >90 days after first-line treatment may benefit from retreatment.

Recommendation 12: Retreat with the same regimen that induced their initial response, usually reinduction with platinum/etoposide.

Strength of recommendation: C

Level of evidence: V

13. Resistant disease

In patients having resistant disease, topotecan improved overall survival compared with best supportive care [31]. No statistically significant difference in median survival was found in a randomised trial comparing topotecan with combination chemotherapy although topotecan caused less toxicity [32]. There is no evidence that combination chemotherapy is superior to single-agent regimens. Both oral and i.v. topotecan had similar efficacy but with slight differences in toxicity [33, 34].

Recommendation 13: Either oral or i.v. topotecan is recommended for selected patients having resistant relapse, i.e. not amenable to reinduction with first-line treatment.

Strength of recommendation: B

Level of evidence: II

14. Refractory disease and beyond second-line treatment

A poor PS, early relapse (within 6 weeks) following first-line treatment [30], and refractory disease are adverse prognostic factors for response and for survival. There is currently no standard second-line chemotherapy regimen for patients who fail to respond to initial treatment (refractory disease) or who relapse shortly after completion of first-line treatment (resistant disease with early relapse) in contrast to resistant disease having late relapse. Active agents from phase II trials include amrubicin, topotecan, irinotecan, paclitaxel, docetaxel, gemcitabine, ifosfamide, and oral etoposide (if etoposide not included in first-line treatment). No drugs have so far been approved by the Food and Drug Administration or the European Medicines Agency for this indication.

Recommendation 14: Selected patients with good PS may benefit from further treatment with a chemotherapy agent not previously used.

Strength of recommendation: B

Level of evidence: III

15. Symptomatic local recurrence in mediastinum

Recommendation 15: Patients, not previously treated with thoracic radiotherapy with a symptomatic recurrence in the mediastinum, such as superior caval vein obstruction or

obstructed major airway, may benefit from thoracic radiotherapy [35–37].

Strength of recommendation: C
Level of evidence: IV

16. Repeat cranial radiotherapy

For recurrence in the brain after PCI or whole-brain radiotherapy, repeat radiotherapy may be useful in carefully selected patients if no systemic treatment options are available [38–42].

Recommendation 16: Local brain re-irradiation, which may include stereotactic radiotherapy, may be considered in selected patients.

Strength of recommendation: C
Level of evidence: V

FUTURE

Several trials could influence treatment options in the near future. These include:

- The CONVERT and CALGB 30610 trials addressing the dose and fractionation issues of concurrent thoracic chemoradiotherapy in limited-stage SCLC.
- The ongoing individual data meta-analysis of early versus late concurrent thoracic radiotherapy and chemotherapy.
- The CREST Dutch trial addressing the role of thoracic radiotherapy in patients with restricted metastatic disease.
- Studies addressing the efficacy of novel systemic treatments, including amrubicin and targeted agents.

acknowledgements

The authors thank Marianne Paesmans of Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium for her great support in methodological aspects during the consensus process. The authors also thank Claire Bramley and all ESMO staff for their support throughout the whole consensus process.

disclosure

Rafal Dziadziuszko (speakers' bureau and advisory board role—Roche, GSK, AstraZeneca); Wilfried Eberhardt (speakers' bureau and advisory board role—AstraZeneca, GSK, Merck Serono, Roche, Novartis, sanofi-aventis, ImClone, Bristol-Myers Squibb, Eli Lilly, Merck USA, Bayer Schering, OSI, Pfizer); Enriqueta Felip (speakers' bureau and advisory board role—Eli Lilly, AstraZeneca, GSK, Merck Serono, Roche, Boehringer Ingelheim); David Gandara (consulting—Amgen, AstraZeneca, Biodesix, Boehringer-Ingelheim, Bristol-Myers Squibb, ImClone, GSK, Genentech, Lilly, Merck, Novartis, Pfizer, Sanofi-aventis); Cesare Gridelli (speakers' bureau and advisory board role—Roche, AstraZeneca, Eli Lilly, Merck Serono); Glenwood D Goss (research funding—Roche Canada); Pasi Jänne (consulting—Pfizer, AstraZeneca, Roche, Genentech, Boehringer Ingelheim; stock ownership—Gatekeeper Pharmaceuticals; other—royalties from patent in EGFR mutation); Tony Mok (honoraria & consulting—AstraZeneca, Roche, Pfizer; honoraria—Eli Lilly, Merck; consulting—Bristol-Myers Squibb, Eisai); Kenneth O'Byrne (advisory board role and research funding—Merck Serono, Roche, AstraZeneca); Robert Pirker (speakers' bureau and advisory board role—AstraZeneca, Eli Lilly, Merck Serono, Roche, Pierre Fabre; advisory board role—Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer); Martin Reck (speakers' bureau & consulting—Hoffmann-La Roche, Lilly, Merck, AstraZeneca; Consulting—Bristol-Myers Squibb); Suresh Senan (research funding—Eli Lilly); Nicholas Thatcher (speakers' bureau and advisory board role—AstraZeneca, Roche, Lilly, Boehringer, Bristol-Myers Squibb); Johan Vansteenkiste (research funding—Eli Lilly, Amgen, AstraZeneca)

The following panel members have declared no conflicts of interest: Paul Baas, Benjamin Besse, Fiona Blackhall, Federico Cappuzzo, Fortunato Ciardiello, Filippo de Marinis, Corinne Faivre-Finn, Martin Früh, Keith M Kerr, Siow Ming Lee, Cecile Le Pechoux, Christian Manegold, Keith McGregor, Luis Paz-Ares, Pieter E. Postmus, Rafael Rosell, Egbert F. Smit, Jens B. Sorensen, Rolf Stahel, Miguel Taron, Jan P. van Meerbeeck, Paul Van Schil, Alain Vergnenegre, Walter Weder.

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appendix

Members of the panel

Prof. L. Crino, D. Gandara, and M. Reck, were unable to attend the conference, but had a major impact on the preparatory work for the conference and on the final manuscript.

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